REMARKS/ARGUMENTS

Claims 1-10, 12, 22, 37-42, 44-54, 56-57, 203 and 204 are currently pending in the application. Claims 4, 8 and 54 are hereby cancelled without prejudice. Claims 11, 13-21, 23-36, 58-202 and 205-213 have been withdrawn without prejudice because they are drawn to a non-elected invention. Applicants respectfully submit that the foregoing amendments to the claims are supported in the application as originally filed and that no new matter has been added. It is believed that no fees are due at this time. In view of the following remarks and amendments, applicants respectfully request a timely Notice of Allowance be issued in this case.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claim 54 was rejected under 35 U.S.C. § 112, first paragraph, for failing to reasonably convey to one skilled in the relevant art that the inventors possessed the invention. Claim 54 has been cancelled. As a result, the rejection of claim 54 is moot.

Claims 1-10, 12, 22, 37-42, 44-54, 56-57 and 203-204 were rejected under 35 U.S.C. 112, first paragraph, for containing subject matter which was not described in the specification to enable one skilled in the art to make and/or use the invention. Claims 4, 8 and 54 have been cancelled. As a result, the rejection of claims 4, 8 and 54 are moot.

The Office asserts that claims 1-10, 12, 22, 37-57 and 203-204 are not enabled because neither the prior art nor the specification teaches how to obtain a variation or codon predictiveness matrix such that variations or polymorphisms may be predicted, specifically how to determine a predictiveness value for a single nucleotide ploymorphism. Applicants traverse the rejection.

Applicants respectfully submit that claims 1, 203 and 204, as amended, are enabled by the specification as originally filed. More specifically, these claims, as amended, recite:

> Claim 1 (currently amended): A method for predicting one or more locations of single nucleotide polymorphisms in a nucleic acid sequence, comprising the steps of:
>
> calculating a variation frequency from a first base to a second base in a dataset of two or more genes;
>
> generating a variation predictiveness matrix from the calculated variation frequency;
>
> comparing the nucleic acid sequence one or more bases at a time with the variation predictiveness matrix to assign a variation value to the bases in the nucleic acid sequence; and

identifying the locations of single nucleotide polymorphisms that will likely cause a variation in one or more bases of the nucleic acid sequence based on the assigned variation value.

Claim 203 (currently amended): A computer program embodied on a computer readable medium for predicting one or more locations of variations in a wild-type gene sequence, comprising:

a code segment for calculating a variation frequency from a first base to a second base in a nucleic acid dataset;

a code segment for generating a variation predictiveness matrix from the calculated variation frequency;

a code segment for comparing the wild-type gene sequence one or more bases at a time with the variation predictiveness matrix to assign a variation value to the bases in the wild-type gene sequence; and

a code segment for identifying one or more locations that will likely cause a variation in one or more bases of the wild-type gene sequence based on the assigned variation value.

Claim 204 (currently amended): A computer program embodied on a computer readable medium for predicting one or more locations of polymorphisms in a wild-type gene sequence, comprising:

a code segment for calculating a variation frequency from a first codon to a second codon in a mutant gene dataset;

a code segment for generating a codon mutation predictiveness matrix from the calculated variation frequency;

a code segment for comparing the wild-type gene sequence one or more codons at a time with the codon mutation predictiveness matrix to assign a variation value to the codons in the wild-type gene sequence; and

a code segment for identifying one or more locations of polymorphisms that will likely cause a variation in one or more codons in the wild-type gene sequence based on the assigned variation value.

With respect to the rejection of these claims, the Office provided the following rationale:

the claims are not enabled because neither the prior art nor specification teaches how to obtain a variation or codon predictiveness matrix such that variations or polymorphisms may be predicted, specifically how to determine a predictiveness value for a single nucleotide polymorphism;

the specification does not teach one skilled in the art how to determine a predictiveness value and/or matrix for predicting one or more locations of SNPs; and

> neither the specification nor the claims discloses how a polymorphism predictiveness value is actually "determined" from the calculated frequency ranges.

Applicants respectfully submit that the amended claims clarify the invention such that the claims are enabled by the application. Claims 1, 203 and 204, as amended, recite that the variation frequency is calculated from a first base [or codon] to a second base [or codon] in a dataset and that the variation predictiveness matrix is generated from the calculated variation frequency. The specification supports this and provides specific examples of these steps. (*see e.g.*, paragraph [0059] (page 21, line 25-page 22, line 9); Tables 1A and 1B). The sequence being studied is then compared one or more bases [codons] at a time with the variation predictiveness matrix to assign a variation value to the bases [codons] in the sequence. The locations of single nucleotide polymorphisms that will likely cause a variation in one or more bases [codons] of the sequence are identified based on the assigned variation value. These steps are also supported in the specification. (*see e.g.*, paragraphs [0065]-[0067] (page 26, line 22-page 27, line 24)). As a result, Applicants respectfully submit that the application enables the claims, as amended.

The Office also stated that "[t]he frequency of a class of mutations which appear in a database is not the same as prediction of the frequency (likelihood?) of a single (point) mutation." Applicants respectfully submit that the present invention does not determine a predictiveness value for single nucleotide polymorphisms within the sequence being studied. Instead, the present invention uses predictiveness values determined from a known dataset to identify locations within a sequence being studied that are likely to produce single nucleotide polymorphisms. In other words, the present invention does not calculate a specific or exact probability for SNPs within a subject sequence; it provides a relative ranking of likely SNPs within the subject sequence. To use an example used by the Office, the present invention can be used to determine the frequency of mutation of CGA to CAA in the HGMD database and then use that frequency to identify locations within a kinase encoding gene that are more or less likely to cause variations in the gene relative to other codons within the gene. As a result, Applicants respectfully submit that the application enables the claims, as amended.

In addition, the Office stated that "[t]he specification teaches that Table 1B (p. 23) is exemplary of a variation predictiveness matrix, but does not teach any specific method steps, statistical analysis, or algorithm for arriving at the 'predictiveness' values of the Table" and "the specification fails to disclose any particular statistical method or algorithm which results in a matrix for predicting SNPs or sequence 'variations.'" Applicants respectfully submit that the following excerpt from paragraph [0059] provides sufficient information to one skilled in the art to calculate the "predictiveness" values listed in Table 1B:

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> The mutations were grouped into classes that are defined by the wild-type and mutant codon pair such "CGA→CAA". There are a total of 3*3*3*64=576 of these classes possible, of these there are 424 codon mutation classes out of the possible 576. Of those classes that are not seen, 14 are rare and 138 are silent. For each mutation class, a predictive value derived from the HGMD data was defined that encompasses: 1) the likelihood that a given point mutation will occur; and 2) the impact of that mutation. For any given class, this predictiveness value, ζ, is that class's frequency in the HGMD, which may be further weighted by codon usage to correct for the fact that certain classes may appear to be frequent only because the wild type usage is high. These values are then normalized to 100.

As previously described, these values are then used to identify locations within a sequence being studied that are likely to produce single nucleotide polymorphisms. Accordingly, Applicants respectfully submit that the application enables the claims, as amended.

The Office also stated that "[p]age 25 and Figure 2 disclose calculation of a distribution of codon mutation classes, but are not exemplary of a variation predictiveness matrix from which SMP's may be predicted." Applicants respectfully submit that the distribution of codon mutation classes on page 25 and Figure 2 are created from the "predictiveness" values of the codon mutation classes within the exemplary variation predictiveness matrix (Table 2). Figure 2A is a distribution of the "predictiveness" values (Table 2) for the codon mutation classes occurring in the HGMD dataset compared to a simulation where all classes are equally likely to occur. Figure 2B is a distribution of the "predictiveness" values (Table 2) for the codon mutation classes occurring in the CFTR gene compared to a simulation where all classes are equally likely to occur. Figure 2C is a distribution of the "predictiveness" values (Table 2) for the codon mutation classes occurring in the Factor IX gene compared to a simulation where all classes are equally likely to occur.

Finally, the Office stated that "the specification does not teach . . . how to determine the 'impact' of the mutation" and "mere frequency does not seem to include or be a determination of impact" and the "likelihood" is calculated nor how to determine the "impact" of the mutation. Applicants respectfully submit that the "impact" is determined from the dataset as explained on pages 21-22 and Table 1A. Accordingly, Applicants respectfully submit that the application enables the claims, as amended.

For each reason described above, Applicants respectfully submit that the claims are fully enabled because one of skill in the art would understand from the disclosure how to perform the elements recited in claims 1, 203, 204 and the applicable dependent claims without undue experimentation. Accordingly, Applicants request the withdrawal of the rejections and allowance of all pending claims.

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Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 9-10, 22, 53 and 54-55 were rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully submit that claims 9-10, 22 and 53 were amended in the previous response to overcome the rejections. In addition, claims 54-55 have been cancelled. As a result, Applicants respectfully submit that these rejections are moot. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112 are respectfully requested.

Conclusion

Applicants respectfully submit that claims 1-3, 5-7, 9-10, 12, 22, 37-42, 44-53, 56-57, 203 and 204, as amended, are fully patentable. Applicants respectfully request that a timely Notice of Allowance be issued in this case. If the examiner has any questions or comments, or if further clarification is required, it is requested that the examiner contact the undersigned at the telephone number listed below.

Respectfully submitted,

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I certify that this paper is being transmitted via facsimile to the USPTO at (703) 872-9306 under 37 CFR 1.8 on the date indicated above.

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